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06/874,992

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STANLEY

DURST 02M

HM12/1119
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EXAMINER

CELSA, B

ART UNIT

PAPER NUMBER

1654

DATE MAILED: 11/19/99

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.
08/874,992

Applicant
Stamler et al.

Examiner
Bennett Celsa

Group Art Unit
1654



☒ Responsive to communication(s) filed on Sep 7, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 15-17 and 49-59 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 15-17 and 49-59 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None, of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 15-17 and 49-59 are currently pending and under consideration.

Withdrawn Objection(s) and/or Rejection(s)

Applicant's cancellation of claims 30-32 in copending Application No. 08/796,164 has overcome the provisional rejection of claims 15-17 under 35 U.S.C. 101 as well as the provisional obviousness double patenting rejection over the copending Application No. 08/796,164.

Applicant's argument that the use of nitroxide hemoglobin as disclosed by Hsia as being outside the scope of the presently claimed invention addressing nitrosated/nitrated hemoglobin has overcome the obviousness rejection of claims 15-17 and 49-52 over Stamler et al, WO 93/09806 (5/93) and Hsia, U.S. Pat. No. 5,591,710 (1/97: filed 8/94 or earlier).

Upon further consideration, the rejection of claims 15-17 and 49-52 under 35 U.S.C. 102(b) as being anticipated by Stamler et al, WO 93/09806 (5/93) is hereby withdrawn..

The obviousness rejections recited in the prior office action have been rewritten in order to better address the newly added claims which are drawn to specific nitrosylated hemoglobin species.

Applicant's argument to the extent relevant to the below new rejections will now be briefly addressed.

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Discussion

Applicant argues that the Stamler reference is not enabled for making S-nitrosylated hemoglobin by arguing that Example 19 is nonenabled for making this compound; citing evidence submitted in the 132 Declaration by Dr. Stamler for support. Further applicant summarizes an interview conducted at the patent office which attempted to further clarify the Declaration evidence.

The Examiner will briefly address some of the issues raised by the Declaration evidence (and arguments).

The first issue raised is the missing reagent issue.

The declarant points out that Example 19 fails to indicate the identity of the nitrating agent which is reacted in equimolar concentrations with hemoglobin (e.g. 12.5 uM at pH 6.9).

However, it is clear that the nitrating agent is SNOAc as recited in the rejection after reading page 58, lines 17-25 and this point is easily confirmed by applicant's own previous application e.g. in Example 1 of 08/559,172, the reaction of SNOAc and hemoglobin in equimolar amounts (and presumably under the same conditions), **achieves the same spectrophotometric evidence** of S-nitrosothiol bond formation. E.g. compare Figures 28 and 29 of WO 93/09806 to Figures 1 and 2 of the 08/559,172.

Accordingly, the WO 93/09806 reference undisputably discloses the reaction of a low molecular weight nitrosothiol (e.g. SNOAC) with hemoglobin.

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Whether applicant actually performed the experiment or the acidified nitrate experiment in his laboratory is irrelevant to the disclosure by the reference of the reaction between SNOAc and hemoglobin.

The Declarant's catching of a mistake with regard to maximum absorbance (e.g. 450nm) when the graph clearly shows a maximum absorbance of 540nm is acknowledged by the Examiner.

However, the declarant's point that one can not measure or distinguish SNO-hemoglobin from hemoglobin at a particular absorbance or that there is not any real confirmation of the presence of SNO-hemoglobin **is not the same as proving the absence of SNO-hemoglobin.**

Applicant's own specification demonstrates that reacting a low molecular weight S-nitrosothiol such as SNOAc in equimolar amounts with hemoglobin (e.g deoxy or oxy) would be expected to generate SNO-hemoglobin (e.g. see present specification at pages 46-48 and Figures 1a-1d).

It is also noted that use of extrinsic evidence by the Examiner to demonstrate inherency is permitted (e.g. see MPEP 2131.01(d)), *including the use of applicant's own specification* (e.g. examples). See *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

The Declarant's attempt to reproduce the Reference Example 19 method was not found persuasive since it is unclear as to whether applicant is showing the absence of SNO-hemoglobin or the inability of the utilized assay to detect the presence of SNO-hemoglobin.

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The Examiner also is unable to reconcile the Declarants' experimental results with those experimental results and statements in the specification which assert that reacting low molecular weight nitrosothiols with oxygenated hemoglobin in 1:1 ratio would form some amount of SNO-hemoglobin (again see specification pages 46-48 and Fig. 1a-1d); and additionally Example 1 and Figures 1 and 2 in application Serial No. 08/559,172 which confirms the presence of a composition which comprises SNO-hemoglobin within the scope of the presently claimed invention.

The Declarant's problem regarding pH and concentration is not seen by the Examiner as problematic where one would be *motivated to increase the amounts of nitrosating agent as pointed out in the rejection below and optimize other reaction parameters (e.g. pH)* as a matter of course and as further motivated by the Stamler reference itself.

It is also noted that the Declarant's and attorneys arguments are not commensurate in scope to the claimed invention; nor do they adequately address the optimization of reaction conditions specifically pointed out in the obviousness rejections below.

Applicant further argues that Stamler does not specifically describe any nitrosated hemoglobin or any effects of nitrosated hemoglobin.

However, as pointed out in the rejections below, the Stamler reference clearly *discloses* the use of nitrosylated proteins generically and nitrosylated hemoglobin specifically to produce the desired effects.

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Applicant's argument regarding the inability of the Stamler reference to enable the making of specifically S-nitrosylated hemoglobin has already been addressed above.

The Examiner again asserts that applicant's claims are not restricted only to the use of an S-nitrosylated hemoglobin compound but are generically broader to include a mixture of S-nitrosylated hemoglobin and other hemoglobin derivatives to which the Stamler reference is enabled by its disclosure and its examples taken separately or in view of obvious modifications thereof (e.g. optimization of reactions and experimental conditions).

Additionally, the Examiner cites support for the proposition that it was well within the ordinary skill of the art to synthesize various nitrosylated hemoglobin compositions.

Applicant's argument that Kaesenmeyer doesn't address hemoglobin is immaterial since it is clear that the obviousness of the claims is dependent upon the combined teaching of the the Kaesenmeyer and Stamler references.

Applicant's summary argument directed to the Greenberg article regarding hemoglobin acting as a scavenger is deficient in several respects.

First, applicant fails to provide explicit support (page and paragraph) for such an assertion.

Second, the Stamler reference teaches pharmaceutical properties possessed by nitrosylated hemoglobin, and not hemoglobin alone. Accordingly, a teaching away with respect to hemoglobin is not germane; and even if germane fails to rebut the evidence provided in the Stamler argument regarding the use generically of nitrosylated proteins to reliably achieve such pharmaceutical properties. Accordingly, the below rejections are hereby maintained.

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New Rejection(s)

2. Claims 15-16, 17 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al, WO 93/09806 (5/93).

Stamler et al. generally teach pharmaceutical deliver of NO by administering nitrosylated protein compounds (e.g. the addition of an NO group to an SH, oxygen, carbon or nitrogen: see page 14, lines 7-12), including nitrosylated hemoglobin, which is formed by conventional means (e.g. see Stamler page 1-5) for use in relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders (e.g. see page 19, lines 22-25; Stamler claims 18, 20, 36, 37, 41-42, 44, 45; etc.). Cardiovascular disorders include those within the scope of the presently claimed invention (e.g. myocardial infarction, pulmonary embolism, myocardial infarction etc. E.g. See page 18, lines 5-11).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize nitrosylated hemoglobin for purposes of inhibiting platelet activation, preventing thrombus formation or for treating platelet activation or adherence disorders including cardiovascular disorders (e.g. infarction, embolism etc.) by administration of nitrosylated hemoglobin to a patient in need thereof as described in the Stamler reference.

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3. Claims 15-16 are rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93) and Kaesenmeyer, U.S.Pat. No. 5,543,430 (8/96: filed 10/94). .

Stamler et al. generally teach pharmaceutical delivery of NO by administering nitrosylated protein compounds (e.g. the addition of an NO group to an SH, oxygen, carbon or nitrogen: see page 14, lines 7-12), including nitrosylated hemoglobin formed by conventional means (e.g. see Stamler page 1-5), for use in relaxing smooth muscle, inhibiting platelet aggregation (e.g. preventing thrombus formation), promoting vasodilation and for treating/preventing cardiovascular disorders (e.g. see page 19, lines 22-25; Stamler claims 18, 20, 36, 37, 41-42, 44, 45; etc.). Cardiovascular disorders include those within the scope of the presently claimed invention (e.g. myocardial infarction, pulmonary embolism, myocardial infarction etc. E.g. See page 18, lines 5-11).

The Stamler reference differs from the presently claimed invention which additionally encompasses the use of nitrated hemoglobin as the NO donor to effect the same function (e.g. relaxing smooth muscle, inhibiting platelet aggregation, preventing thrombus formation, promoting vasodilation and for treating/preventing cardiovascular disorders).

However, the Stamler reference, besides generically describing the use of nitrosylated proteins (e.g. nitrosylhemoglobins), additionally suggests the use of S-nitrosylhemoglobin, for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders

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The Stamler et al. generic teaching of using NO donor nitrosylated protein compounds, including nitrosylated hemoglobins and methemoglobins, and a species of specifically nitrosylated hemoglobin (e.g. S-nitrosylated) would motivate one of ordinary skill in the art to utilize other nitrosylated hemoglobins which would be deemed to be functionally equivalent as NO donating compounds.

Thus, the selection of a species of NO donating hemoglobin is a matter of choice to one of ordinary skill in the art since the Stamler reference teaches the functionally equivalent use of nitrosylated proteins, including hemoglobins, as well as individual nitrosylated hemoglobin species including thionitrosylated hemoglobin.

In this regard, the use of oxidized forms of NO (e.g. nitrites/nitrates) as functionally equivalent NO donors is conventionally known in the art (E.g. See Kaesenmeyer at col. 6).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to substitute nitrated hemoglobins for nitrosohemoglobins in the methods as disclosed by Stamler with a reasonable expectation of success due to functional equivalency of nitrites/nitrates as NO donating compounds.

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4. Claims 15-17 and 49-59 are rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93) alone and if necessary further in view of the specification admission as to prior art on pages 37-39, Kaesenmeyer, U.S.Pat. No. 5,543,430 (8/96: filed 10/94), Moore et al., J.Biol. Chem. Vol. 251, No. 9, (5/76) pages 2788-2794, Sharma et al., J. Biol. Chem. Vol. 253, No. 18 (9/78) pages 6467-72 and Chem. Res Tox. 1990 Vol. 3, pages 289-291.

Stamler et al. generally teach pharmaceutical delivery of NO by administering nitrosylated protein compounds (e.g. the addition of an NO group to an SH, oxygen, carbon or nitrogen: see page 14, lines 7-12), including nitrosylated hemoglobin formed by conventional means (e.g. see Stamler page 1-5), for use in relaxing smooth muscle, inhibiting platelet aggregation (e.g. preventing thrombus formation), promoting vasodilation and for treating/preventing cardiovascular disorders (e.g. see page 19, lines 22-25; Stamler claims 18, 20, 36, 37, 41-42, 44, 45; etc.). Cardiovascular disorders include those within the scope of the presently claimed invention (e.g. myocardial infarction, pulmonary embolism, myocardial infarction etc. E.g. See page 18, lines 5-11).

Additionally, the Stamler reference, besides generically describing the use of nitrosylated proteins (e.g. nitrosylhemoglobins), additionally suggests the use of S-nitrosylhemoblin, for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders, the Stamler reference fails to disclose other specific species nitrosylated hemoglobins (e.g. nitrosylhemoglobin, polynitrosated hemoglobin, and nitrosated methemoglobin).

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Further, Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNO_2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);
2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

as well as Example 19 with respect to hemoglobin (e.g. See Example 19 on pages 58-59), which utilizes selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) as nitrosating agent.

Optimization, e.g. using “excess nitrosating agent” or higher pH values (e.g. pH 7.4) than that utilized in the specific thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is within the skill of the art and is further suggested by Stamler since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31). See also other Examples which utilize physiological conditions in analogous steps. E.g. page 30, lines 20-27; page 33, lines 20-26).

Additionally, the specification summary of the prior art on pages 37-39 disclose art-recognized techniques for formulating various oxidized and deoxidized nitrosylated hemoglobins in which hemoglobin is nitrosylated on different portions of the compound.

Similarly, the Chem. Res Tox. 1990 Vol. 3, pages 289-291 reference discloses a method of transferring the nitrosyl group to sulfur (as well as oxygen, nitrogen and sulfur) of heme proteins, including hemoglobin to thus form, polynitrosated hemoglobins, including SNO-hemoglobins.

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Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize oxidized/deoxidized S-nitrosylated hemoglobin for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders as suggested by the Stamler reference.

Although, the Stamler reference, generically describes the use of nitrosylated proteins (e.g. nitrosylhemoglobins), and suggests the use of S-nitrosylhemoglobin, for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders, the Stamler reference fails to disclose other individual species of nitrosylated hemoglobins (e.g. nitrosylhemoglobin, polynitrosated hemoglobin, and nitrosated methemoglobin).

However, the formation of nitrosated hemoglobins, including, oxidized/deoxidized nitrosylhemoglobin, polynitrosated hemoglobin, and nitrosated methemoglobin is within the skill of the art. E.g. See Stamler reference on pages 1-5 ; specification admission on pages 37-39; and Moore et al. and Sharma et al. disclosing "stock nitrosylhemoglobin" which comprises nitrosyl-deoxyhemoglobin.

Further, the Stamler et al. generic teaching of using NO donor nitrosylated protein compounds, including nitrosylated hemoglobins and methemoglobins, and a species of specifically nitrosylated hemoglobin (e.g. S-nitrosylated) would motivate one of ordinary skill in the art to utilize other nitrosylated hemoglobins which would be deemed to be functionally equivalent as NO donating compounds for use in relaxing smooth muscle and inhibiting platelet aggregation.

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Thus, the selection of a species of NO donating hemoglobin is a matter of choice to one of ordinary skill in the arts since the Stamler reference teaches the functionally equivalent use of nitrosylated hemoglobins including thionitrosylated hemoglobin.

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize oxidized/deoxidized S-nitrosylated hemoglobin as well as other nitrosylated hemoglobin species (e.g. polynitrosated hemoglobin, nitrosylhemoglobin) for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders since these other nitrosylated hemoglobin species would be expected to act equivalently as NO donating compounds.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703)308-4028.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa



November 18, 1999

**BENNETT CELSA
PRIMARY EXAMINER**